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STRONTIUM

A STUDY IN PHYSIOLOGICAL THERAPEUTICS.

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of Philadelphia.

THE following research primarily grew out of a curiosity to know the action of the soluble strontium salts upon the circulation, but during the attempt to gratify this curiosity the subject grew somewhat apace, until in its final form it has seemed to us best to divide the resulting article into two parts: first, physiological; second, clinical.

PART I. PHYSIOLOGICAL.

In most of the experiments the strontium lactate was used, but the nitrate was also employed both in experiments upon the frog's heart and also in those upon the circulation in the mammal. As no difference could be made out in the qualitative influence of the two salts, and as the quantitative difference is very slight, we shall in this report use the term "strontium" or "strontium salt" as indifferently referring to the nitrate or the lactate. The nitrate contains about 8.5% more of strontium than does the lactate, and this difference is scarcely greater than the difference in the individual susceptibility of animals of the same species. In all of the experiments upon mammals, unless it is otherwise stated, the strontium salt was given intravenously and usually in a 20% solution.

One series of experiments was made upon the uninjured animal, without artificial respiration, in order to determine the general influence of the drug. The results in the various experiments were almost

identical, and are portrayed in the following tabulated statement of one experiment.

EXPERIMENT No. I.

YOUNG WHITE DOG.

Weight, 10,216 kilos. 20% Strontium Lactate Solution.

Time.	Injection.	Pulse.	Arterial Pressure	Remarks.
4.43.30	. . .	180	138	Dog very hard to keep quiet.
4.44	5 cc.	. . .	. . .	
4.44.30	. . .	66	170	Enormous pulse-waves.
4.47	. . .	87	170	Waves not quite so large { syst 100. diast. 70.
4.48	. . .	69	164	
4.49	5 cc.	. . .	. . .	Struggling.
4.50	. . .	57	154	
4.52	. . .	60	156	
4.53	. . .	156	171	Pulse-waves much smaller { syst. 91. diast. 80.
4.53.30	. . .	156	171	
4.54	. . .	72	147	Pulse-waves very large { syst. 100. diast. 47.
4.56.30	. . .	54	134	Enormous pulse-waves { syst. 114. diast. 20.
4.57	5 cc.	. . .	. . .	
4.58	. . .	165	154	
4.59	. . .	75	136	
5.04.30	. .	162	154	
5.04.50	5 cc.	. . .	. . .	
5.06	. . .	204	142	
5.09	. . .	264	165	
5.14	. . .	150	144	
5.16	. . .	150	140	
5.25	. . .	78	79	

As shown in the report of the experiment just given, the most characteristic effect of the strontium salt is to decrease excessively the pulse-rate, while at the same time it notably increases the arterial pressure. The detail of the action of the strontium, however, is much better portrayed in the various tracings in our possession than can be readily given in a tabulated statement. These tracings show that in the earlier portions of an experiment after each injection of the strontium there is a brief period of rise of arterial pressure with rapid heart-beats and pronounced respiratory curves, the pulse-waves at this period not being in any way remarkably large. After a short time the characteristic effects of the drug become pronounced in the disappearance of the respiratory curves and in the appearance of most extraordinary cardiac beats, with large diastoles and great exhibition of power; so that the pulse-waves may

extend over as much as 80 or 90 millimeters, the mean arterial pressure during all this time remaining much above the normal.

This phenomenon of quick, rather small pulse, followed by slow enormous pulse, was usually repeated after various injections, until finally a condition was reached in which the individual pulse-waves were steadily many times larger than the normal, although the arterial pressure was greatly below the normal. In some cases, however, the phenomena were different, the individual injections failing to produce the temporary quick small pulse at a time when the pressure was still much above the normal. In some instances the change from an enormous pulse-wave to the short quick cardiac movement occurred spontaneously, that is, without any appreciable cause, disappearing as abruptly as it had come on, after a continuance of some seconds, no reasons for its going off any more than for its coming on being apparent. Finally, when the injections were sufficiently repeated, the pulse-waves became very slow and the pressure gradually fell to near zero.

Having made out the effects produced by the injection of soluble strontium salts into the circulation, we next made a series of experiments to determine whether these effects are due to the immediate action of the strontium salt, or whether they are secondary to some influence exerted upon the respiratory centers. For this purpose a number of experiments were made with the use of artificial respiration in curarized animals. In these experiments the effect of the drug upon the pressure was pronounced, but the influence in lessening the pulse-rate, though it was often manifested, was on the whole certainly less distinct and active than in the normal animal. The following tabulated report of one of these experiments fairly represents the whole series.

It may be concluded from our experiments that the soluble strontium salts, while usually slowing the pulse and increasing the size of the pulse-wave, by a direct action in some way cause a great rise of the arterial pressure, which is followed, if the dose has been sufficient, by a pronounced fall of the arterial pressure, this being usually accompanied with a rapid

pulse, ending in complete extinguishment of the arterial pressure and of the heart's beat. Careful examination of our tracings made with and without artificial respiration, shows that the action of the drug upon the pulse is much less uniform than upon the pressure, singular variations occurring in the rate of the heart-beat, without corresponding alterations of the arterial pressure.

EXPERIMENT No. II.

Dog.

Curarized. Artificial Respiration. Weight, 9,240 kilos.
Strontium Nitrate 20% Solution.

Time.	Injection.	Pulse.	Arterial Pressure.	Remarks.
12.03	. .	132	143	
12.03.38 } 12 03.40 }	3 cc.	. . .	. . .	
12.03.35	. . .	. . .	. . .	Pressure began to fall.
12 03.42	. . .	. . .	. . .	Pressure began to rise.
12.09	. .	114	157	
12.09.25 } 12.09.34 }	2 cc.	. . .	. . .	
12.09.44	. . .	120	134	
12 11.30	. . .	114	161	
12.18	. . .	84	202	Pulse-waves very large.
12.27	. . .	192	132	
12.27 38 } 12.27.48 }	1 cc.	. . .	. . .	
12.28	. . .	186	110	
12.28.30	1 cc.	. . .	. . .	
12.29.10	. . .	192	134	
12.34	. . .	192	106	Feeble heart-beat.
12.34.20	2 cc.	. . .	. . .	
12.34.40	. . .	. .	96	Pressure fell to 96.
12.35	. . .	. . .	. . .	Clot.
12 37	. . .	192	76	
12.37.20	2 cc.	. . .	.	
12.37.40	2 cc.	. . .	. . .	Pressure fell slightly after each injection.
12.39	2 cc.		. . .	
12.39.20	. . .	156	68	
12 40	. . .	156	64	
12.41.20	5 cc.	. . .	.	
12.41.40	. . .	162	48	Very irregular heart.
12.42	2 cc.	. . .	. . .	
12.47	. . .	132	42	
12.47.30	2 cc.	. . .		No effect.
12.48.20	5 cc.	. . .	. . .	
12.48.50	. . .	.	32	Heart-beat could not be counted.
12.49.30	. . .	108	56	Good pulse-waves.
12.51.20	5 cc.	. . .	.	Followed by a fall.
12.55.10	5 cc.	. . .	. . .	Followed by fall.
12.56	. . .	102	43	Rate very irregular.
12.58.10 } 12.58. :0 }	5 cc.	. . .	. . .	
12.58.40	. . .	. . .	. . .	Heart almost stopped.
12.58.40	. . .	. . .	. . .	Cut right vagus.
12.58.50	. . .	. . .	.	Cut left vagus.
12.59	. . .	54	46	Irregular pulse.
1.02	. . .	. . .	. . .	Pulse regular and strong.
1 06	. . .	120	42	Regular.
1.06.30	10 cc.	. . .	. . .	Pressure fell to 0.

It is evident that many of the changes produced by strontium in the pulse are secondary, and we have not carried our work far enough to be able to elucidate the nature of the secondary influences or the absolute method in which the drug affects the pulse. In one or two experiments it was found that section of the vagi, after the free use of strontium nitrate had reduced the pulse from 240 to 226, was followed by immediate rise of the pulse-rate, the pulse-rate, however, not reaching the normal number; so that it would appear that there is a double influence at work in the production of the slow pulse; one influence being direct upon the heart itself, one upon the inhibitory nerves. In another experiment, however, after section of the vagi in the curarized animal with artificial respiration, the injection of the strontium lactate failed to reduce the pulse-rate, although the injections were repeated until the arterial pressure was finally almost abolished. It is evident that in order to determine the exact influence of the drug upon cardiac inhibition further work is required.

In order to determine how far the rise of pressure is produced by an action upon the vasomotor centers three experiments were made upon animals after high-up section of the cord. In the first of these experiments made upon a dog, the first 2 injections were followed by a rise of the arterial pressure, amounting to nearly 50%; but the third injection was followed by immediate fall of the arterial pressure, which continued under the subsequent use of injections until death. The same rate of slowing of the pulse-beat and increased size is shown in the tracing, as was noted when the cord was not cut, only the pulse-waves were much smaller when there was no spinal section. The character of the effect was identical, the apparent intensity not so great.

In the second experiment the strontium produced increase of the arterial pressure without slowing of the pulse. The third and fourth experiments we give in tabulated form.

The experiments which have just been recorded demonstrate that section of the spinal cord, and consequent separation of the bloodvessels from the domi-

RABBIT.

Weight, 1,605. Cord cut. Fourth cervical. Strontium nitrate.

Time.	Pulse.	Arterial Pressure.	Remarks.
12.52	270	87	
12.52.30	. . .	. . .	Injected 2 cc. into carotid.
12.52.40	. . .	60	Pulse fell at once.
. . . .	. . .	. . .	Pulse very slow.
12.52.45	. . .	. . .	Pulse rising rapidly.
12.52.45	270	108	
12.53.30	270	82	
12.53.40	. . .	. . .	Injected 5 cc., followed by slowing pulse and fall, then a momentary rise; then fall.
12.55	. . .	108	Rose again to 108, then rapidly fell to 0. Pulse-waves so small they could not be counted.

DOG.

Weight, 8,740. Cord cut. Fourth cervical. Artificial respiration.

Time.	Pulse.	Arterial Pressure.	Remarks.
12.11	132	96	
12.11.20	. . .	. . .	Injected 5 cc.
12.12.10	102	117	
12.14	96	100	
12.14.30	. . .	. . .	Injected 3 cc.
12.15.30	96	118	
12.19.30	96	97	
12.19.40			Injected 5 cc.
12.21	108	105	

nating vasomotor center in the medulla, does not prevent the production of a marked rise in the arterial pressure by the strontium salt; and demonstrates therefore that the strontium salt causes a rise of the arterial pressure by an action exercised upon the heart itself, or upon the nervo-muscular apparatus in the walls of the bloodvessels.

Our next series of experiments were directed to determine whether the strontium salts do or do not act upon the nervo-muscular apparatus in the walls of the bloodvessels. They were made upon frogs whose brain and spinal cord had been destroyed, and into whose aorta and sinus venosus cannulas had been placed. Artificial serum was forced into the aortic cannula at a constant pressure, 0.6% of saline solution, and the same saline with 0.5% of strontium lactate being alternately used. After each use of the strontium lactate

the vessels were well washed out with normal saline solution. The drops from the venous cannula were allowed to fall upon the end of a lever so arranged as to record on a drum each drop as it fell. The various experiments were all concordant in showing that the strontium markedly decreases the rate of flow. Of one of these experiments we give the following record:

	Drops per Minute.		Drops per Minute.		Drops per Minute
Saline	80	Saline	23	Saline	18
Strontium . . .	52	Strontium . . .	6	Strontium . . .	5

As the strontium salts, under the circumstances named, diminish the rate of transmission of the blood through the peripheral vessels, and as there seems to be little reason for supposing that this is due to any mechanical alteration of the fluid, it is a fair conclusion that these salts cause contraction of the capillaries by a direct action upon them.

To determine the cardiac action of the drug a series of experiments were made with Kronecker's apparatus, bovine serum diluted with normal saline solution being used; in which also the strontium salt employed was dissolved. Three experiments were made with

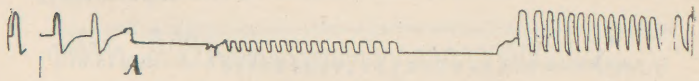

FIG. 1.—Frog's heart. Before *A*, normal; after *A*, 0.5% solution strontium nitrate.

the isolated heart of the frog, both auricles and ventricles being preserved and the heart beating spontaneously. In the first of these experiments (Fig. 1), the application of 0.5% strontium solution was followed by a brief period of rapid, greatly diminished beat, ending in a short period of arrest, followed by an enormous increase in the size of the cardiac beat, as well as in its rate.

In the second experiment (Fig. 2), a much weaker solution, about 0.1% of the strontium lactate was employed. Its use was followed by an immediate slowing of the cardiac rate, with a marked increase in the height and amplitude of the pulse-wave; as time pro-

gressed the pulse gradually became smaller and quicker, until the cardiac movements yielded no further tracing than that of a line with very small rapid

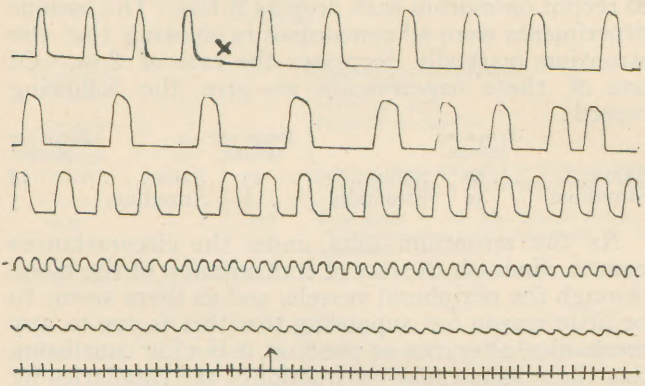

FIG. 2.—Frog's heart. Before *x*, normal; after *x*, 0.1% solution of strontium. As only a portion of the record is shown, the whole time of use of strontium is longer than indicated by second marks.

waves. The third experiment gave results entirely similar to those just noted.

On examining the tracings which we have reproduced, it will be seen that in both of the experiments

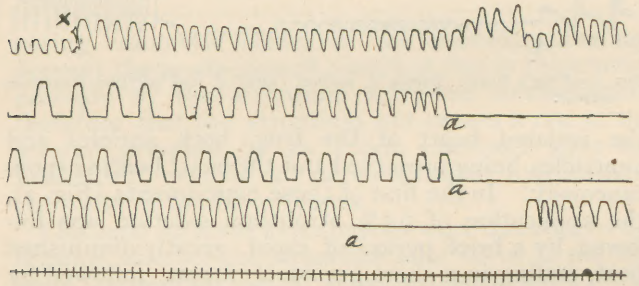

FIG. 3.—Showing effect of 0.5% solution strontium lactate on apex of frog's heart. Single induction shock, 1 per second; before *x*, normal; after it, solution. As only part of record is here, time of strontium is longer than appears in second mark. *a*, stimulation stopped.

the cardiac beats after the use of the strontium frequently failed to reach the abscissa line, and that not infrequently there were no distinct diastolic pauses;[1]

[1] These effects were more plain in the original tracings than in the reproduction, though they do show in the latter.

evidences that under the action of strontium the dilation of the heart was not complete.

The next experiment was made with the apex of the frog's heart, entirely separated from the auricle. (Fig. 3). Stimulation was produced by a single induction shock, at the rate of 1 per second. A 0.5% solution of the strontium lactate was used. The immediate effect of the strontium lactate was to increase enormously the height and size of the cardiac waves without producing at first any slowing of the beat; after some seconds there was a brief period of digitalis-like apical spasm, with an enormous rise in the cardiac pressure and failure of complete diastotic relaxation. Shortly after this 20 seconds of rest was given to the heart; when stimulation was resumed

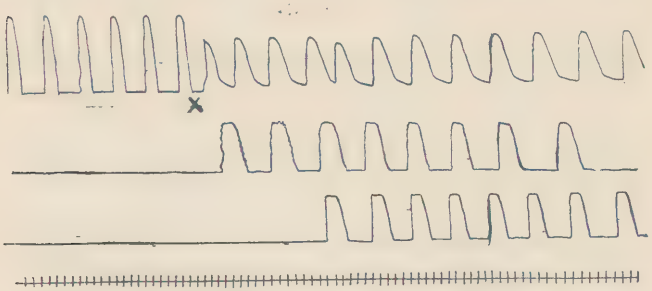

FIG. 4.—Atropinized frog's heart. *x*, 0.5% solution of strontium salt.

the cardiac beats were found to be very much slowed, and enormously increased both in height and amplitude, as shown in Fig. 3.

The third series of experiments with the isolated frog's heart were made with atropin and strontium. When (Fig. 4) the 0.5% solution of the strontium salt was applied to the thoroughly atropinized heart there was an immediate alteration in the character of the cardiac wave; it became less high but much broader, with much less sharply marked diastolic pauses. There was at first no slowing of the cardiac rate, but after a time this slowing became very pronounced. On the other hand, when (Fig. 5) atropin was applied to the thoroughly strontiumized heart, no distinct effect was produced.

These experiments seem to us to demonstrate, first, that the soluble strontium salt influences directly the frog's heart; increasing, when the dose is very small, the height and the duration of the muscular contraction, lessening or altogether putting an end to the

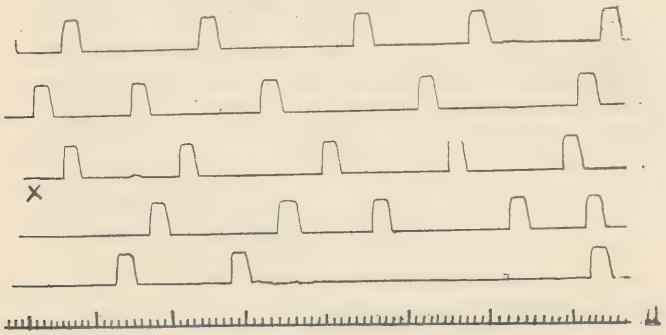

FIG. 5.—Frog's heart under influence of 0.5% solution strontium nitrate. *x*, solution of atropin sulphate applied.

diastolic pauses and at times causing apical spasm of the heart, the rate of the heart's beat being slowed; but that large doses increase the rapidity of the pulsation, but progressively diminish the size of the cardiac waves until cardiac arrest occurs. Second, that this action of strontium is directly upon the car-

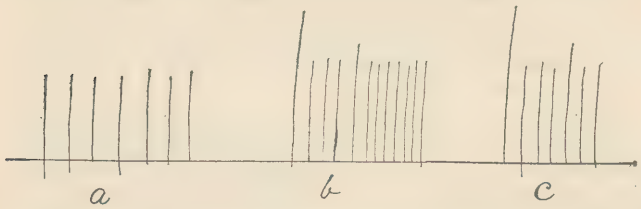

FIG. 6.—Showing action of strontium nitrate, 0.02% solution on gastrocnemius of frog. *a*, normal; *b*, after 1 minute of solution; *c*, after 5 minutes. Maximum induction-shocks.

diac muscle itself, the result being fully as great with the separated cardiac apex responding to induction shocks, or with a whole heart in which the inhibitory apparatus has been paralyzed by atropin, as with the normal isolated heart.

According to the statements of Lauder Brunton in his work on Pharmacology and Therapeutics, strontium diminishes the contractile power of the muscles, as shown by the height of the muscle-curve; while at the same time it increases the length of the contraction. This statement of course suggested that the action of strontium upon the heart and the vessel-walls, which we have demonstrated to exist, is only a part of the wider action upon the general muscular system. We here reproduce two tracings (Figs. 6 and 7) which show that while the extremely minute dose of strontium increases the height of the muscular contraction, the larger dose, as stated by Dr. Brunton, greatly lessens and finally abolishes the contractile power. In the tracing, Fig. 7, it will be seen that though a 0.5% solution of strontium was sufficient to reduce

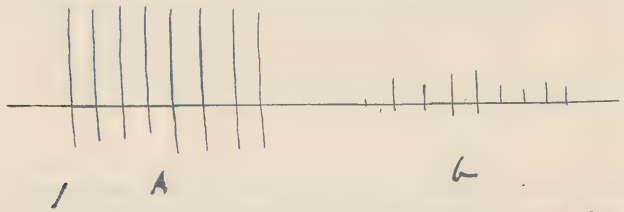

FIG. 7.—Showing action of strontium nitrate, 0.1 solution, on muscle of frog, induction shock. *a*, normal; *b*, after 5 minutes' immersion.

the height of the curve distinctly it greatly widened the base of the curve, that is, lengthened the contraction of the muscle.

It is evident that a drug which not only increases the power, but which especially prolongs the contraction-period of the muscle-fiber, if it acts on the muscle-fiber in the wall of the capillaries in the same way it does upon the voluntary muscle, must enormously increase the resistance to the passage of the blood by contracting the bloodvessels. We have proved that by a local action, strontium does lessen the lumen of the capillaries and increases the resistance to the passage of the blood, so that it appears to be an inevitable conclusion that strontium acts upon the muscle-fibers in the vessel walls as it does upon those of the voluntary muscles. We believe that we have demonstrated

in the early part of this research that strontium acts directly upon the heart and upon the capillary, and our curves show (see Figs. 3, 4, 5), at least so far as the heart is concerned, that the action of the drug upon the muscle of the heart is similar to that which it has upon the voluntary muscles; so that the conclusion is fully reached that strontium is *a muscle-poison which stimulates the muscle and afterwards paralyzes it, and that its stimulating effect upon the circulation is the result of the widespread general influence of the drug on the muscle-fibers both of voluntary and involuntary life.*

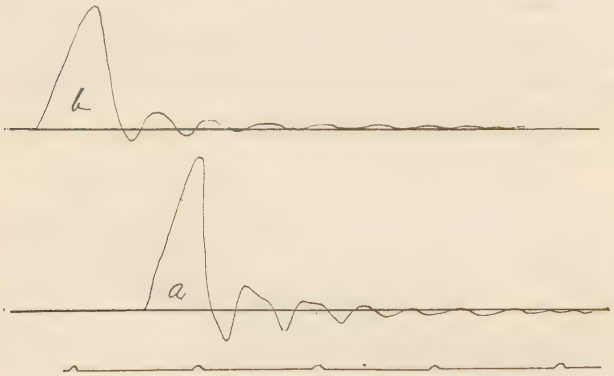

FIG. 8.—Showing character of contractions after 0.5% solution of strontium nitrate; gastrocnemius of frog. *a*, normal; *b*, after strontium.

PART II. CLINICAL.

The physiological results reached by us naturally have suggested that the soluble strontium salts may be valuable in the treatment of cardiac diseases accompanied with loss of power in the circulation, and have led to a consequent test of their therapeutic activity in 6 cases of organic heart-disease.

In the first case there was mitral and aortic regurgitation, with dilatation, pronounced failure of compensation, irregular pulse, dyspnea, and edema of the legs. Strontium nitrate was given in doses of 30 grains every 4 hours, increased after a time to 30 grains every 2 hours, but no perceptible effect was produced. On the substitution of tincture of digitalis marked relief was obtained in a very short time.

The second case was one of mitral regurgitation, with failing compensation, cough, dyspnea, cardiac pain, and irregular small pulse. To this patient 30 grains of the strontium nitrate was given every 4 hours, without the production of other effect than a slight increase in the amount of urine daily secreted. Subsequently the use of digitalis was followed by a favorable response.

Case 3 was one of cardiac dilatation, with mitral regurgitation, failing compensation, cough, distinct cyanosis, edema of the legs, and feeble pulse. Strontium nitrate, 20 grains, was given, at first every 4 hours, subsequently every 2 hours, without appreciable effect. Five minims of the tincture of strophanthus given every 4 hours brought great relief.

Case 4 was one of mitral stenosis, with aortic and mitral regurgitation. There was dyspnea, cough, edema of the feet, and secondary albuminous urine with casts. Strontium nitrate, 30 grains, given every 4 hours, increased to 40 grains every 2 hours, had no effect. The strontium was then administered by hypodermic injection into the buttocks in normal salt-solution, 10 grains every 4 hours. The injections caused so much irritation that they were of necessity stopped after 3 days. No effect was produced unless it were some increase in the amount of urine and lessening of albumin. Relief was subsequently slowly obtained by the free use of digitalis and strychnin with Basham's mixture.

Case 5 was one of mitral regurgitation, with edema, cyanosis, high-colored urine containing a trace of albumin, and other evidences of failing compensation. Strontium nitrate, 20 grains, was given every 2 hours, increased to 40 grains every 2 hours, without effect. Subsequently 5 drops of the tincture of strophanthus administered every 4 hours gave relief.

Case 6 was one of aortic obstruction and regurgitation, with marked dyspnea and edema of the lower extremities. Strontium nitrate, 20 grains, was given every 4 hours, increased to 1 dram every 4 hours without any perceptible result. Relief was obtained by the use of strychnin and strophanthus.

In each of the above cases the use of the strontium was maintained from 4 to 14 days; the patient was kept in bed, the pulse taken every hour, and the urine systematically measured. The drug was well received by the stomach, but no effects of any kind could be observed, except that in 2 cases there was a slight increase in the amount of urine passed, and in one case a decrease in the percentage of albumin. In the case in which the salt was given hypodermically no effect upon the rate, regularity, or strength of the pulse could be detected after the single dose, or as the result of the treatment.

The therapeutic trials which we have made with soluble strontium salts are, we think, sufficient to

show that it is without value in the treatment of cardiac disease. This clinical conclusion is in apparent contradiction to the results which we have reached physiologically; but it must be remembered that in our experiments upon the lower animals the drug was given intravenously. January, 1898, a paper on the absorption and elimination of strontium was published by Dr. Horatio C. Wood, Jr., in which the conclusion was reached that the soluble salts of strontium are not eliminated after their administration by the mouth or their hypodermic use, and are probably not absorbed to any considerable extent. Thus, after 3 grams of the strontium lactate had been given hypodermically to a small dog, the urine and feces were separately collected for 72 hours and carefully analyzed without any strontium being detected; while after taking by the mouth of 3 grams of the strontium lactate 10% of the amount ingested was recovered from the feces during 3 days, and even a trace of strontium could be detected in the urine only the first day. It is further worthy of remark that in this experiment, 7 times the amount of strontium that was obtained on the second day was recovered from the feces on the third day; so that it is evident that the strontium was slowly working its way through the alimentary canal.

Professor John Marshall suggested that, when the strontium salt is taken by the mouth, absorption takes place to some extent in the stomach, but that portion of the salt which escapes into the intestines is converted into an insoluble phosphate.

In order to test the question of the absorption and elimination of the strontium salts we have made a number of studies upon human beings and the lower animals.

CASE 7.—Child 6 years of age, under treatment for subacute Bright's disease; had been taking for more than a week, by injection into the colon, 30 grains of strontium lactate daily. The urine collected for 24 hours contained 0.2 gram of the strontium salt.

CASE 8.—Miss V. C., aged 10, suffering from Friedreich's ataxia; general health good. One dram strontium lactate was given daily, in powder, by the mouth in divided doses (20 grains

after each meal), from February 26 to March 1, inclusive. The whole of each 24 hours' urine was saved and examined.[2]

Date.	Quantity Urine.	Strontium. Present = +. Absent = —.	Quantity Strontium. Estimated as Sulphate.	Remarks.
Feb. 20	. . . . .	—	. . . . .	Daily dose 5j.
Feb. 27	420 cc.	—	Not weighable.	
Feb. 28	530 cc.	+	0.03.	
March 1	750 cc.	+	0.02 estimated.	Part of weight lost.
March 2	240 cc.	. . .	. . . . .	
March 3	Lost because of diarrhea.	. . .	. . . . .	
March 4	400 cc.	+	Not weighable.	
March 6	450 cc.	+	Not weighable. Trace only.	
March 7	450	+	Slight trace only.	
March 8	420	+	Slight trace only.	
March 9	225	—	No evidence of strontium by spectroscope or flame.	

The results of the chemical studies which have just been made are in accord with the results previously reached by Dr. Horatio C. Wood, Jr., in showing that when a soluble salt of strontium is taken by the mouth it does not escape to any extent from the body with the urine and is probably not absorbed except in minute amount.

Thus in Case 8 it was not until 3 grams daily of the strontium had been given for 2 days that the strontium could be detected in the urine, and that after the second day after the cessation of administration only traces of the element could be detected, total disappearance occurring in the week.

In Case 7, 2 grams had been given for many days by the colon and yet only 0.2 gram could be obtained from the urine.

The suggestion of Professor Marshall that the salts are converted into insoluble phosphates in the alimentary canal may have some basis of truth, but at best represents only a small portion of the story.

When strontium salicylate is added to a very weak solution of hydrochloric acid, decomposition commences at once. The precipitation can be dis-

[2] All of the tests for strontium were made, viz: Urine evaporated to dryness, organic matter oxidized; potassium nitrate residue dissolved in HCl; strontium and calcium precipitated by adding NH_4Cl (to keep Mg. in solution), then NH_4OH to alkaline reaction, the $(NH_4)\ C_2O_3$, which precipitated strontium and calcium as carbonates. Filtered, washed, and strontium and calcium carbonate dissolved in HCl. Solution evaporated to dryness and tested by flame-test and spectroscope. Strontium precipitated by $Ca\ SO_4$ solution and weighed as sulphate.

tinctly seen when there is only 0.05% of hydrochloric acid present in the solution; and when the acidity reaches 0.1% practically all of the salicylic acid comes down at once. As this degree of acidity is considerably below the normal acidity of the gastric juice, it seems certain that the decomposition of the strontium salicylate begins, if indeed it be not completed, in the stomach; a conclusion which is confirmed by the results of the analysis in Case 9.

An examination of the following table will show that urine passed a half-hour after the ingestion of a gram of strontium salicylate gave an active reaction of salicylic acid.

CASE IX.—Adult in Good Health.

	Date.	Voided Urine.	Amount.	Salicylic Reaction in Urine.	Strontium Reaction in Urine.
I	Feb. 11	9.45 A.M.	Unnoted.	Took Strontium Salicylate 1 gram.	
	" 11	10.15 A.M.	50 cc.	Good Reaction.	Trace of Strontium shown by flame-test and spectroscope. Quantity not weighable.
	" 11	11.15 A.M.	143 cc.	" "	
	" 11	1.20 P.M.	155 cc.	" "	
II	" 11	6.45 P.M.	130 cc.	" "	No Stront. detected.
III	" 11	6.45 A.M. to	1000 cc.	" "	" " "
	" 12	10.00 A.M.			
	" 12	10.00 A.M.	500 cc.	Fair "	" " "
IV	" 12	12.00 NOON.	1000 cc.	Slight "	" " "
	" 12	7.30 P.M.	500 cc.	Absent.	" " "
V	" 12	10.00 P.M.	450 cc.	"	" " "
	" 13	9.00 A.M.	450 cc.	"	" " "
	" 13	3.00 P.M.	250 cc.	"	" " "

Any soluble strontium salt which would through capsulation or other cause escape decomposition in the stomach would meet in the intestinal tract alkalies, and perhaps phosphates or other compounds, which would rapidly decompose it. The form of precipitation may vary in individual cases, but it is evident that an insoluble precipitate must in all cases occur; and our experiments seem to have demonstrated that it is not possible to obtain through the alimentary tract sufficient absorption of strontium to produce any systemic effect.

There is, however, a possible fallacy underlying the experiments which we have made. It may be that the strontium nitrate is largely eliminated by the intestines. The experiments of Dr. Horatio C. Wood, Jr., show that when taken by the mouth it does escape with the stools; but of course any substance, taken by the mouth and not absorbed, must pass out with the feces. In order to settle the question, Dr. H. C. Wood, Jr., injected 3 grams of strontium lactate hypodermically into a dog, and upon examination of the urine and feces, separately collected for 72 hours after the injection, failed entirely to discover the strontium.

So far as this experiment goes, it would seem to show that strontium given hypodermically is not absorbed. In order to further test the matter, we made the following experiment:

STRONTIUM NITRATE HYPODERMATICALLY.

Experiment with Bitch.

Feb. 24.—9 A.M. Injected 2 grams strontium nitrate.
" 25.—4 P.M. Had passed no urine nor feces. Expressed 35 cc. urine from bladder, which contained .005 strontium, weighed as sulphate.
" 27.—500 C.C. urine contained .015 strontium weighed as sulphate.
" 25 and 26.—*Feces.* Strontium sulphate, *0.2036.*
Urine collected for next 10 days, and examined for strontium. Only a trace found in total quantity.

This experiment certainly shows that the nitrate of strontium given hypodermically is absorbed to some extent, and is eliminated more largely from the intestinal tract than with the urine. As, however, the whole amount eliminated was only about one-tenth of that given hypodermically, it is evident that absorption was very slow and imperfect. When it is further remembered that in all our experiments, as well as those of Dr. H. C. Wood, Jr., strontium disappeared from the urine within a very short time after its ingestion, unless there had been long-continued administration, it seems to us evident that only a very small amount of strontium can be absorbed from the alimentary canal.

The hypodermic method of administration is attended with so much local irritation as to forbid its practical use. In our experiments upon the bitch

there was considerable local sloughing; and in our trials upon man the local pain and inflammation forced the discontinuance of the hypodermic administration. Our studies upon Master ——, Case 7, indicate that when strontium salts are exhibited continuously for a length of time, continuing absorption leads to some accumulation in the system, which in turn produces persistent elimination through the kidneys. Even in such cases, however, the amount of strontium in the blood is never, when ordinary therapeutic doses are used at least, sufficient to produce any evidences of systemic action, but it is plain that the metal may exert a local influence at the point of elimination; so that the clinical conclusions reached by various medical practitioners, that the soluble strontium salts are useful in chronic Bright's disease, is not antagonized or contradicted by this research. In the light of our own experience with disease, however, many of the statements made in the medical journals in regard to the great value of these salts in renal affections, appear exaggerated.

It is worthy of remark that the urine of the child to whom the lactate was given by the bowels, yielded much more of the strontium than did that of the child who received the salt by the mouth. This would indicate that absorption takes place more freely from the large intestine than from the stomach, but may possibly have depended upon the longer continuance of the exhibition of the drug in the first case mentioned.

Finally, it is evident that in many cases the strontium acts simply as a vehicle for the carrying of acid into the system of the substances with which it is combined. Thus, in the case of the strontium salicylate, separation of the acid from the base begins in the stomach, while the strontium compound, passing into the intestinal tract, long remains there, and according to clinical experience acts beneficially upon digestion. This local influence is probably parallel to that of bismuth, except that it is probably less astringent. The insoluble salt, clinging by its weight and mechanical properties to the mucous membrane, yields with extreme slowness to decomposition and absorption, and exerts a long-continuing local influence.